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July 26, 2011 By: Misty Prasad

Date Misty Prasad

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Stefan Schorling	) EXAMINER: David C. Thomas
SERIAL NO.: 10/587,386	) ART UNIT: 1637
FILED: May 3, 2007	) CONFIRMATION NO: 4893
FOR: **NEW PRIMERS AND PROBES FOR THE DETECTION OF PARVOVIRUS B19**	) DOCKET NO. 22398-US

APPLICANTS' APPEAL BRIEF

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REAL PARTY IN INTEREST

The real party in interest is ROCHE MOLECULAR SYSTEMS, INC., 4300 Hacienda Drive, Pleasanton, California, 94588 USA, the assignee of record, which is a subsidiary of F. Hoffmann-La Roche AG, Grenzacherstrasse 124, 4070 Basel, Switzerland.

RELATED CASES: APPEALS AND INTERFERENCES

None

CLAIM STATUS

1-3. Cancelled

4. Rejected *

5. Rejected

6. Rejected

7. Rejected

8. Rejected

9. Rejected

10. Rejected

11-14. Cancelled

15. Rejected

16. Rejected

17-24. Cancelled

*** CLAIM 4 is subject to this Appeal.**

STATUS OF AMENDMENTS

Applicant's amendments filed on October 7, 2010 with the response to a non-final rejection were ENTERED by the examiner.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is a method for the detection of parvovirus B19 nucleic acid sequence in a sample by nucleic acid amplification with the primer pair SEQ ID NO: 15 and SEQ ID NO: 17 and detection with the probe SEQ ID NO: 11.

Claim 4 (the only independent claim pending) is provided below along with exemplary references to the specification pages and paragraphs. (Numbers are referenced from the published application US 2007/0281294.)

4. A method for the detection of a target nucleic acid comprising the nucleic acid sequence of parvovirus B19 in a sample **{PAGE 2 [0009]}**, comprising;

(a) providing a sample suspected to contain the target nucleic acid, **{PAGE 2 [0010]}**

(b) providing a pair of primers **{PAGE 2 [0011] and PAGE 11 [0132]}** comprising a first primer consisting of SEQ ID NO: 15 **{PAGE 2 [0022] and PAGE 11 [0132]}** and a second primer consisting of SEQ ID NO: 17, **{PAGE 2 [0022] and PAGE 11 [0132]}**

(c) amplifying the target nucleic acid, **{PAGE 2 [0012]}**

(d) contacting the sample with a probe under conditions for binding the probe to the target nucleic acid, {**PAGE 2 [0018]**} the probe consisting of SEQ ID NO: 11 {**PAGE 10 [0122]**} and

(e) detecting the binding product between the target nucleic acid and the probe as an indication of the presence of the target nucleic acid. {**PAGE 2 [0019]**}

GROUNDS FOR REJECTION TO BE REVIEWED

- Whether **claim 4** is obvious under 35 U.S.C. §103(a) over Schmidt et al. (Vox Sanguinis (2001) Vol.81, No.4, pp.228-235) and/or over Harder et al. (J. Clin.Microbiol. (2001) Vol.39, No.12, pp.4413-4419), in view of Hemauer et al. (J. General Viology (1996) Vol.77 pp. 1781-1785), and further in view of Lowe et al. (Nucleic Acids Res. (1990), Vol. 18, No.7, pp.1757-1761).

All other pending claims are dependent upon claim 4 and will not be argued separately in this brief.

ARGUMENT

I. JURISDICTIONAL STATEMENT

The Board has jurisdiction of this appeal under 35 U.S.C. §134(a).

The final rejection Notification date was December 23, 2010, setting a three-month deadline for reply on March 23, 2011. With a one-month extension of time, the applicants filed a Notice of Appeal under 37 CFR §41.31(a)(1) with a Pre-Appeal Brief Review Request on April 25, 2011. The Notice of Panel Decision from Pre-Appeal Brief Review was mailed on May 27, 2011, resetting the deadline to submit an appeal brief at June 27, 2011. With a one-month extension, the brief is being timely filed by July 27, 2011.

II. A *PRIMA FACIE* CASE OF OBVIOUSNESS HAS NOT BEEN ESTABLISHED FOR CLAIM 4

Independent claim 4 was rejected as obvious under 35 U.S.C. §103(a) over Schmidt and/or Harder, in view of Hemauer, and further in view of Lowe.

The Examiner has asserted, in part, that while the prior art does not teach the use of primers or probes consisting of the sequences as cited in the pending claims, both Schmidt and Hemauer teach primers that were used in PCR amplification of the NS1 region of parvovirus B19 and therefore are useful for detection of this target sequence in a sample. (Final action 12/2010 page 14) Further, the Examiner asserts that one of ordinary skill in the art would have been motivated to modify the methods of Schmidt and/or Hemauer along with the other cited art to use primers of SEQ ID NOS: 15 and 17 and a probe sequence of SEQ ID NO: 11. The Examiner asserts that the skilled artisan would have had a reasonable expectation of success in modifying the methods of Schmidt and/or Hemauer to substitute for similar and equivalent primers and a probe derived from the same well-known and amplifiable conserved stretch of the

NCS-1 region, resulting in the predictable amplification and detection of multiple different parvovirus sequence variants. The Examiner has asserted that the claimed primers and probe simply represent structural homologs, or "equivalents", which are derived from sequences suggested by the prior art, and that the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

THE HISTORY OF APPLICANTS ARGUMENTS

Applicants have argued that none of the cited references alone or in combination teach the specific sequences SEQ ID NOS: 15, 17 and 11, or the combination of these sequences, as provided in the pending claims. In addition, Applicants have shown:

1. there was no motivation for one skilled in the art to modify Schmidt in view of Hemauer or Harder to achieve this specific combination of oligos as claimed, and in fact Hemauer teaches away from designing primers in this region,
2. the Examiner has misused the terms "homologs" and/or "equivalents" in the present context of nucleic acid amplification,
3. the selection of the claimed sequences was not "obvious to try", nor was there a reasonable expectation of success.

A *PRIMA FACIE* CASE OF OBVIOUSNESS OF CLAIM 4 HAS NOT BEEN ESTABLISHED

1. Schmidt, Hemauer and Harder

The Examiner has asserted that Schmidt, Hemauer and Harder teach PCR primers to amplify the NS1 region of parvovirus B19, noting that "additional optimization may be required ... which may require trying other primers". (Final Action 12/2010 page 15) As presented in Applicant's prior responses, one of ordinary skill would NOT have been motivated to modify the method of Schmidt simply because of the fact that others also amplify areas of the NS1 region. This region spans > 2KB which offers an almost infinite number of possible alternative oligo sequence design options. There is no motivation provided in either Schmidt, Hemauer or Harder to make primers in different locations of the NS gene other than the specific locations presented in their publications; neither Schmidt nor Hemauer nor Harder discuss the need to improve or change the sequences provided. In fact Hemauer teaches the amplification of 4 distinct regions of the genome, not just NS, and does not provide evidence that one particular region should be selected away from the other 3 to detect parvovirus. Hemauer teaches that many of these regions are more highly conserved than the region targeted by Schmidt, essentially "teaching away" from designing new oligos in the region used by Schmidt. Applicants have asserted that it is unreasonable to design and test every oligonucleotide possible in a >2kb region, without direction to do so, to achieve the claimed sequences.

The Examiner further asserts that Hemauer teaches a conserved stretch of sequence at position 2020-2240, and therefore one of skill would recognize that amplification and detection of such a conserved region would allow for detection of parvovirus. (Final Action 12/2009 page 7 and page 12) Applicants agree that one of skill in the art of designing nucleic acid amplification and detection systems would look to a region of sequence conservation in which to design the oligonucleotides. However, Hemauer teaches that this particular amplification region 2020-2240 is only "relatively conserved" in contrast to some of the other regions

discussed in the publication. This region showed 12 exchanges, or base differences/changes, in the limited sample set provided (only 20 patients). Applicants note that Hemauer's own NS oligos are designed OUTSIDE of this supposedly "conserved" region. Hemauer also provides that "the region from nt 2985-3170 was highly conserved, and only a few nucleotide changes could be identified (3 in 185 bp)." (Hemauer page 1784, top of right column) Hemauer goes on to teach that other regions had even less exchanges when described at a protein level, and that changes are not equally frequent within all isolates. Additionally Hemauer notes that "all isolates exhibited changes in their DNA sequences". (Hemauer page 1783 right column). No statistical analysis is provided showing if any of these base differences are even significant in this small sample size. Applicants assert that the Examiner is in error in drawing the conclusion from the limited data set in Hemauer that position 2020-2240 is the most conserved region of the parvovirus genome. In fact, based on the relatively low number of base changes found in region 2985-3170, Hemauer teaches away from using the NS region because one of skilled in the art would have had a greater motivation to design primers in the 2985-3170 region than in the NS region.

As the Examiner himself noted in the Final Office Action dated 12/23/10, the Supreme Court said, in *KSR*, "When there is a *design need* or *market pressure* to *solve a problem*, **and** there are a *finite number of identified, predictable solutions*, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." 127 S.Ct. at 1742. The Examiner has not identified a problem inherent in the prior art, has not shown any design need or market pressure to solve that problem, and has not demonstrated the necessary finite number of identified, predictable solutions to the problem. The Federal Circuit, in applying *KSR* to the case of *Esai Co. Ltd. v. Dr. Reddy's Laboratories*, held that:

> "The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue

> potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. (*Citation omitted.*) Third, the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S.Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed.Cir. 2008), this court further explained that this "easily traversed, small and finite number of alternatives ... might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."
> *Esai Co. Ltd. v. Dr. Reddy's Laboratories*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

Therefore, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness, because he has not demonstrated why one of ordinary skill would be motivated to design the specific oligonucleotides or combination thereof presented in the instant invention.

2. Homologs and Equivalents

The Examiner has asserted that the use of "structural homologs" means that equivalency has been recognized in the prior art since SEQ ID NOs 11, 15 and 17 are homologous to sequences taught by Hemauer. (Final Action 12/2010 page 16) As detailed in prior responses, Applicants has asserted that the claimed oligos and those taught by the cited art are not "homologous".

The following table (as provided on page 6 of the 2010 RCE) summarizes the NS region oligos as taught by Schmidt (page 229 last paragraph) and Hemauer (Table 2), in comparison to the oligos as provided in the instant invention:

	Claims	Schmidt	Hemauer
Upstream primer/ location	SEQ ID NO: 15 2044-2064	TP1 2030-2048	F1 1817-1833
Comparison to claimed SEQ:	-	***15 bases away*** ***5 bases (25%) overlap***	***211 bases away***
Downstream primer/ location	SEQ ID NO: 17 2193-2174	TP2 2171-2151	B1 2500-2517
Comparison to claimed SEQ:	-	***23 bases away***	***307 bases away***
Probe/ location	SEQ ID NO: 11 2070-2095	Probe 2050-2073	(NA)
Comparison to claimed SEQ:	-	***22 bases away***	***na***

Similarly, Harder Table 1 provides sequences that are directed to the NS region positions 1420-1631. These sequences are greater than 400 bases away from the sequences of the instant invention.

At best, Schmidt provides oligo TP1 which overlaps SEQ ID NO:15 by 5 bases (25%); all other oligos, including those of Harder, have 0% match and are located 22-400, or 2000+ bases away. Different oligo sequences that bind throughout the >2KB region are definitely NOT "equivalents". It is well known to those of skill in the art that designing oligonucleotides to bind to viral sequences is complicated by the viral sequence diversity; this sequence diversity is appreciated by the cited prior art, for example Hemauer teaches sequence variability and conservation compared to a consensus sequence (as discussed above). Oligos that hybridize to an area of the virus that is highly divergent will not "perform" as well as oligos that hybridize to an area of sequence conservation.

The Examiner asserts that the claimed primers and probe simply represent structural homologs, or "equivalents", which are derived from sequences suggested by the prior art. (Final Action 12/2010 page 5) Applicants assert that the Examiner is in error in citing **MPEP 2144.06** "Substituting equivalents for the same purpose":

> "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).
> An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Schmidt, Hemauer and Harder all teach sequences directed to various parts of the viral genome; throughout the references it is discussed how the various sequence regions are different from each other and offer better/worse targets for oligonucleotide design and viral detection. It is inherent in the art that all oligonucleotide sequences <u>are not created equal</u> – they do not all perform equivalently. Therefore the Examiner is in error in regarding all oligonucleotides that bind to the Parvovirus B19 genome to be "equivalents".

The term "structural homolog" is discussed in MPEP 2144.09 *Close Structural Similarity Between Chemical Compounds (Homologs, Analogues, Isomers).* MPEP 2144.09 II provides: "Compounds which are ...homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See also *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers *prima facie* obvious). Here, homologs are presented in the context of chemical structure; this type of structural relationship does not apply in the context of nucleic acids because, as discussed above, all nucleic acid sequences are not equivalent. Therefore, in the context of nucleic acids, homology must refer to a "degree of similarity between the sequences" and NOT the fact that they can hybridize to the same virus. As discussed above, the art cited by the Examiner provides sequences which are <u>different than</u> and <u>completely distinct from</u> the sequences provided in the instant invention. Oligonucleotides that bind to the same gene tens or hundreds of bases apart do not possess similar properties and are NOT homologs. An example of homologs in the context of a nucleotide sequence would be two hypothetical oligonucleotides such as illustrated below:

1) 5'-AACATTGGCTAAAAGCTTAA-3'

2) 5'-ATTGGCTAAAAGCTTAACGC-3'

These 2 oligonucleotides have similar properties in that they would hybridize to the same sequence area, since they have the same 17 of 20 bases (85%) and share a structural similarity. In this case, based on sequence 1) a biochemist of ordinary skill in the art may be motivated to design "homologous" sequence 2), which is just shifted to the 3' end by a few bases.

However, the oligonucleotides of the instant invention do not share such similar properties with the sequences provided in the prior art. All but 1 of the sequences of the instant invention have <u>zero homology</u> to the sequences of the cited prior art; SEQ ID NO: 15 has a 25%

match to Schmidt primer TP1. This 25% match represents only 5 base pair similarity, and one skilled in the art would recognize that 2 sequences with such a low similarity would not be considered "homologous". As discussed above, the parvovirus NS1 region is greater than 2 KB. Oligonucleotides that bind to different parts of this 2000 base pair region are definitely NOT "equivalents" nor are they "structural homologs" The Examiner has over-generalized the terms of homologs and/or equivalents in the present context of nucleic acid amplification.

3. Obvious to try

The Examiner has asserted that the present invention was "obvious to try" based on the fact that Schmidt teaches oligos within 23 bases of the claimed oligos, and the fact that Hemauer teaches the sequence of the region. (Final Action 12/2010 page 17) As detailed above and in prior responses, none of the cited prior art provides specific direction to design alternative oligos or direction as to which of many possible choices of oligonucleotide design is likely to be successful in the methods as presently claimed. Hemauer teaches a broad range of sequences in the >2KB NS1 gene, many of which are more highly conserved than the region targeted by Schmidt, essentially "teaching away" from designing new oligos in the region used by Schmidt. There are no problems or technical hurdles provided in Schmidt left to be solved ("...the assay is highly reproducible..." Schmidt p. 230 top right column) that would have motivated one skilled in the art to alter the oligos in Schmidt to arrive at the presently claimed invention.

The Federal Circuit (Kubin 561 F.3d 1359) has "outlined two classes of situations where 'obvious to try' is erroneously equated with obviousness under § 103." The first situation is applicable here, wherein the invention is not obvious under 103 when:

> "...to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful results, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful", (*O'Farrell*, 853 F.2d 894).

It was not obvious to select SEQ ID NOS: 15, 17 and 11 or the combination thereof from the large number of possible oligonucleotides and combinations from the parvovirus genome. In the absence of specific direction from the prior art, it was not "obvious to try" the claimed sequences. The "obvious to try" standard is not applicable in this case.

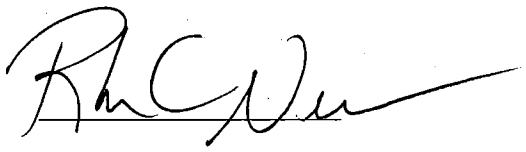
Further, the Examiner has asserted that the teachings of Lowe provide guidance for designing primers; in combination with the cited art, one of skill will have a reasonable expectation of success in amplification of the NS1 region using equivalents of the claimed primers. Applicants repeat the assertions above including the Examiner's incorrect use of "equivalents" in the context of nucleic acid sequences, and to the lack of teaching and motivation in the cited art in selecting the particular region of the >2KB area in which to design oligos to achieve the claimed SEQ ID NOS: 15, 17 and 11 of the invention.

III. CONCLUSION

Applicants submit that the rejections of claim 4 under 35 U.S.C. § 103(a) should be withdrawn, and such action of the Board is respectfully requested. All of the pending dependent claims depend from claim 4, so the arguments presented in relation to claim 4 apply equally to the dependent claims.

Applicants respectfully request a 1-month extension of time to submit this Appeal Brief. The response date was June 27, 2011 (one month after receipt of decision from Pre-Appeal Conference); with the granting of this request, the response time is re-set to July 27, 2011. The commissioner is hereby authorized to charge the amount of $130, the fee due under 37 CFR §1.17(a)(1) and the amount of $540, the fee due under 37 CFR 41.20(b)(2) to Deposit Account No. 50-0812. The Commissioner is hereby authorized to charge any additional required fees to Deposit Account No. 50-0812.

Respectfully submitted,



Date: July 26, 2011

Rhea C. Nersesian (Reg. No. 55,488)

Roche Molecular Systems, Inc.
4300 Hacienda Drive
Pleasanton, CA 94588
Tel: (925) 730-8566
Fax: (925) 225-1128

APPENDIX

I. CLAIMS

1-3. (cancelled)

4. (rejected) A method for the detection of a target nucleic acid comprising the nucleic acid sequence of parvovirus B19 in a sample, comprising;

(a) providing a sample suspected to contain the target nucleic acid,

(b) providing a pair of primers comprising a first primer consisting of SEQ ID NO: 15 and a second primer consisting of SEQ ID NO: 17 ,

(c) amplifying the target nucleic acid,

(d) contacting the sample with a probe under conditions for binding the probe to the target nucleic acid, the probe consisting of SEQ ID NO: 11 and

(e) detecting the binding product between the target nucleic acid and the probe as an indication of the presence of the target nucleic acid.

5. (rejected) The method according to claim 4 wherein the probe carries a label.

6. (rejected) A method according to claim 5 wherein an additional probe carrying a label is contacted with the sample in step d) so that a pair of probes consisting of a first and a second probe is contacted with the sample in step d).

7. (rejected) The method according to claim 6

wherein said amplifying step c) comprises contacting the sample with the said pair of primers to produce an amplification product if the target nucleic acid is present in said sample,

wherein said step d) comprises contacting said sample with the pair of probes, wherein the members of said pair of probes hybridize to said amplification product within no more than five nucleotides of each other, wherein the first probe of said pair of probes is labeled with a donor fluorescent label and wherein the second probe of said pair of probes is labeled with a corresponding acceptor fluorescent label;

and detecting the binding product between the target nucleic acid and the pair of probes in step e) by detecting the presence or absence of fluorescence resonance energy transfer between said donor fluorescent label of said first probe and said acceptor fluorescent label of said second probe, wherein the presence of fluorescence resonance energy transfer is indicative of the presence of the target nucleic acid in the sample, and wherein the absence of fluorescence resonance energy transfer is indicative of the absence of the target nucleic acid in the sample.

8. (rejected) The method according to claim 4 wherein the probe carries a first label and a second label.

9. (rejected) The method according to claim 8, wherein the target nucleic in step c) is amplified with a template-dependent DNA polymerase.

10. (rejected) The method according to claim 9, whereby the binding product between the target nucleic acid and the probe in step (e) is detected by the quantity of the first

label or the second label that is released from the probe hybridized to the target nucleic acid by exonuclease hydrolysis by the template-dependent DNA polymerase.

11-14. (cancelled)

15. (rejected) A method according to claim 4, wherein the primer and/ or the probe comprise a modified nucleotide or a non-nucleotide compound.

16. (rejected) A method according to claim 4, wherein other target nucleic acids are detected in the same reaction.

17-24. (cancelled)

II. EVIDENCE

None

III. RELATED PROCEEDINGS

None